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(54) Title: VEHICLE FOR DELIVERING ACTIVE PHARMACEUTICAL INGREDIENTSTO THE H UMAN SKIN

(57) Abstract

A new and improved vehicle for delivering pharmaceutical ingredients to the human skin in a manner whereby the bioavailability, subcutaneous adsorption, and effectiveness of the active ingredient are remarkably enhanced. The vehicle comprises a volatile silicone, a fatty alcohol having from 12-22 carbon atoms, a preselected active ingredient; and such preservatives or emulsifying agents as may be warranted.

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Description

Vehicle for Delivering Active Pharmaceutical Ingredients to the Human Skin

Technical Field

This invention relates to topical compositions and more particularly to a new and improved vehicle for delivering topically applied pharmaceutial ingredients in a manner whereby the bioavailability and effectiveness of the active ingredient is remarkably enhanced.

Background Art

The prior art has traditionally delivered topically effective pharmaceutical agents in creams, lotions and gels, all of which require the user to soil his fingers and hands in the application of such medicaments and in the subsequent action of "rubbing it in". Further, such products are greasy, slow to dry and inevitably leave a residue which not only is visible, but rubs off onto clothing and the like, all of which are discomforting to the social ease of the user.

One variation from the traditional creams, lotions and gels occurred with the development of the so-called stick delivery systems which were used to apply anti-perspirants, deodorants, lip balm, lip coloring and like ingredients which are generally applied to the surface of the skin.

Antiperspirant sticks based on the combination of a volatile silicone, a fatty alcohol and a powdered antiperspirant were recently developed and marketed. These sticks, however, have not been extended beyond simple antiperspirant sticks using water soluble inorganic antiperspirant salts. This limited use is the result of the known mechanism of antiperspirant vehicles and the need to intentionally design such delivery systems so as to limit the amount of active ingredient (antiperspirant) which can penetrate into the skin. For an antiperspirant to be efficacious, a large concentration of the active ingredient must be maintained on the surface of the skin from whence it is slowly dissolved and diffused into the apocrine ducts, rather than being absorbed through the skin. To extend this prior art to other pharmacologically active topical agents, it is necessary to greatly enhance the amount of the drug which is able to penetrate through the skin to reach the desired sites of action. This absorption of a drug through the skin is referred to as percutaneous absorption.

Nor does the typical lip balm formulation solve the problem because such products normally contain large amounts of wax (such as Beeswax, Carnauba, and the like), and oils, (such as, castor oil, lanolin and the like), whereupon a greasy/oily sensation is created on the skin which is not only unpleasant but gives the user the feeling of being "dirty". In addition, this type of formulation, as with antiperspirants, severely limits the percutaneous absorption of most drugs through the skin.

Likewise, the conventional creams and lotions fail to obviate the problems enumerated because the

creams and lotions are excessively greasy and have the potential to sequester the active ingredient so that the percutaneous absorption of the drug and its efficacy is reduced.

Disclosure of Invention

One object of the present invention is to develope a consumer acceptable delivery system for applying pharmaceuticals to the human skin which avoids the aforesaid disadvantages of the prior art creams, lotions, gels and sticks while enabling the user to readily control its application to a specified location with maximum effectiveness, a minimum of waste, and no mess.

Another object of the present invention is to provide a new and improved delivery system which is compatible with a broad range of effective pharmaceuticals and is capable of delivering such pharmaceuticals with high efficiency and increased percutaneous absorption thereby increasing both the bioavailability of the active ingredient and its efficacy.

Best Mode for Carrying Out the Invention

The present invention relates to a semi-solid vehicle for applying a pharmaceutical agent to the human skin and comprises a volatile silicone, such as dimethicone and cyclomethicone; a fatty alcohol having from 12 to 22 carbon molecules or a mixture of C_{12} to C_{22} fatty alcohols; a preselected active ingredient; and such preservatives, or emulsifying agents as may be warranted.

An important factor of the present invention is the use of a volatile silicone such as dimethicone,

the cyclomethicones or equivalent cyclic silicones, which avoid the heavy oils and waxes heretofore employed and provide instead a silky and non-greasy lubricant which enables the active ingredient to be spread evenly and smoothly upon the skin. Once the active ingredient has been delivered to the selected site, the silicones will volatilize and leave no residue on the skin. Suitable silicones for use herein are available commercially from Dow Corning as 200 fluid (0.65cs), 344 fluid (formerly Q2-1053) and 345 fluid (formerly F1-3597).

The use of Dodecanol, Tridecanol, Tetradecanol, Pentadecanol, Hexadecanol (cetyl alcohol), Heptadecanol Octadecanol, Nonadecanol, Eicosanol, Heneiconsanol, and Docosanol (Stearyl alcohol) or mixtures thereof provide another important feature of the invention.

Specifically the basic system of the present invention contains from about 20% up to about 40% (w/w) of fatty alcohol such as a mixture of stearyl and cetyl alcohol; from about 30% up to about 60% (w/w) volatile silicone such as dimethicone or a cyclomethicone; from about 0.1% up to about 10% (w/w) of an active drug reagent; and from about 1% to about 10% of various other ingredients such as preservatives, and/or emulsifying agents.

The system thus described has the further surprising advantage in that it is not limited just to water soluble drugs but can also be employed in a most propitious manner with many insoluble ingredients when suspended in a fine particulate form (less than about 30 μm) to form an acceptable product.

The specific details whereby our system is employed with specific pharmacological agents shall now be described. Special attention is directed to the ability of this system to stabilize a number of drug ingredients which are known to be unstable in most common vehicles, and to accept those active ingredients which heretofore have not been acceptable in any effective vehicle systems.

Active pharmaceutical ingredients which are effectively incorporated into the present delivery system and which, as will be demonstrated, exhibit improved stability and enhanced bioavailability are listed in Table I. The accepted use of each ingredient and its expected shelf-life, as determined by accelerated stability studies, are also reported in Table I.

TABLE I

INGREDIENT	USE	EXPECTED SHELF-LIFE*
Hydroquinone 2%	Skin Bleaching	24-36 months
Benzoyl Peroxide 5%	Acne Treatment	24 months
Coal Tar Extract 2%	Psoriasis Treatment	36 + months
Hydrocortisone .5%	General Steroid	24-36 months
Providone-Iodine 1%	Antiseptic Product	24-36 months
Bactimycin .5%	Antibiotic Product	24-36 months
13-Cis Retinoic Acid .1%	Acne Treatment	18-24 months

(*Note: When formulated in accordance with present invention.)

From Table I, it can be readily seen that the volatile silicone based vehicle system of the present invention provides an excellent matrix for the stabilization of many drugs that are known to

decompose in aqueous vehicles or easily oxidize in creams and lotions.

The silicone/fatty alcohol (C_{12}-C_{22}) system of the present invention further offers a vehicle of low-irritancy potential. This is important in treating skin disorders or sensitive skin with any cosmetic agent or drug. Many of the vehicles currently used contain ethyl alcohol, isopropyl alcohol, glycols and other moderately irritating substances. The silicone/fatty alcohol system provides a non-stinging, non-irritating and low allergenic vehicle.

The increased biovailability of the hydroquinone stick of this disclosure when compared to the more traditional vehicles such as creams and lotions, is a unique result. It is commonly known, in comparing the efficacies of different antiperspirant vehicles, such as creams, aerosols, roll-ons and sticks, that the determining factor is the level of the active ingredient (antiperspirant). That is, the same percentage of active antiperspirant ingredient will produce the same level of antiperspirant effect; regardless of the vehicle used.

As shown in Tables II and III, the present invention demonstrates a substantially improved drug bioavailability, and therefore efficacy, over the other commonly used vehicles containing the same percentage of active ingredient (e.g., hydroquinone). In addition, the present invention demonstrates a substantially greater bioavailability than a standard cream vehicle containing over twice the active ingredient. These results are remarkable in comparison to what would be expected by simply utilizing the prior antiperspirant technology.

In one practice of the present invention using stearyl alcohol, all of the desired ingredients with the exception of the volatile silicone are mixed together and the mixture is then heated gently to about 80°C until all of the ingredients are thoroughly mixed throughout the melted stearyl alcohol (MP=80°C). The melted solution or suspension is then cooled to 60-70°C and the volatile silicone is added to the cooled mixture and stirred thereinto. When the silicone is thoroughly mixed throughout, the resulting mixture is poured into suitable molds or containers and allowed to cool until solidified. A propitious effect of this practice is that the active ingredient maintains its homogeneous dispersion throughout the solidified mass and there is little or no settling therein.

The invention has been successfully practiced to produce the stick compositions reported below which are then capable of delivering the noted active pharmaceutical ingredient to the desired sites in an easy and efficient manner.

The user employs the resulting stick by grasping the container in which the vehicle with its active ingredient has been disposed. The conventional push-up container, that is, a container having a base plate which is upwardly mobile in response to a force applied thereto by the consumer, which in turn forces the vehicle upwardly until an applicator surface is exposed above the upper rim of the container, can be considered to typify the container used herein. The user then manipulates the container in a stroke-wise fashion to paint the desired location with the mixture thereby delivering the active ingredient to the situs where its action is desired or required.

This, of course is not intended to limit the use of the present invention to only stick forms, but is presented as an example of one potential use.

To further aid in the understanding of the present invention, and not by way of limitation, the following examples are presented.

EXAMPLE 1

A batch of a hydroquinone-containing vehicle is prepared to provide a product for the treatment of hyperpigmentation. Note that such a product, to be effective, must be capable of penetrating the epidermis to reach the hyperactive melanocytes positioned at the dermal/epidermal junction.

A mixture of hydroquinone, benzophenone-3, Octyl Dimethyl-para-amino-benzoic acid, Laureth-4, stearyl alcohol, cetyl alcohol, PEG-1000, and preservatives are stirred together and gently heated to 80°C where it is maintained while all of the ingredients are thoroughly blended throughout the molten mass. The molten solution/suspension is then cooled to a temperature between 60-70°C and a volatile silicone (cyclomethicone) is added thereto and blended therein. After the silicone is thoroughly mixed with all of the other ingredients, the mixture is poured into a cylindrical mold or container and cooled further until it is completely solidified.

The resulting product, herein denominated "hydroquinone stick" has the following analysis (in weight percent):

2.0%	Hydroquinone
3.0%	Benzophenone-3
7.0%	Octyl dimethyl-PABA
4.0%	Laureth-4
20.0%	Stearyl Alcohol

5.0% Cetyl Alcohol
.3% Various preservatives
6.0% PEG-1000
52.7% Volatile Silicone

EXAMPLE 2

A hydroquinone stick was prepared according to EXAMPLE I. A product was produced having the following composition (in weight percent):

2.0% Hydroquinone
3.0% Benzophenone-3
7.0% Octyldimethyl PABA
4.0% Ethoxy Ethanol
.3% Various Preservatives
10.0% PEG - 1000
30.0% Stearyl Alcohol
44.7% Volatile Silicone

EXAMPLE 3

The hydroquininone sticks prepared according to Example 1 was tested for bioavailability against the major commercial OTC products sold for skin bleaching using the standard protocol for such tests based on FICK'S Law (see: Franz, T.J., "On the bioavailability of topical formulations .... " J.Amer. Academy of Dermatology, St. Louis, Vol 9, No 1, pp 63-73 at 68-69). The results are reported in Table II, and expressed as the percent of the applied dose absorbed over 24 hours.

TABLE II

Product	Manufacture	Vehicle	% Active	% absorbed in 24 hours
Esoterica®	Norcliff	Cream	2.0%	2.5
Porcelana®	J.Martin Inc.	Cream	2.0%	2.0
Faience®	Lee Pharm.	Lotion	2.0%	2.0

Example 1	Stick	2.0%	28.0
Example 2	Stick	2.0%	32.0

EXAMPLE 4

Repeating the procedure of Example 3, the hydroquininone stick of Example 1 was tested for bioavailability against the major ethical pharmaceutical (Rx) cream for treating skin hyperpigmentation. The results of this test appear in Table III.

TABLE III

Product	Manufacture	Vehicle	%Active	% absorbed in 24 hours
Eldoquin	Elder Pharm.	Cream	4.0%	15.0
Example 1		Stick	2.0%	32.0

EXAMPLE 5

A benzoyl peroxide stick was prepared using the procedures described in Example 1. A product was produced having the following composition (in weight percent):

6.4%	Benzoyl peroxide - (78% Active)
3.0%	Laureth-4
4.0%	PEG-1000
23.0%	Stearyl Alcohol
6.0%	Cetyl Alcohol
.3%	Various preservatives
57.3%	Volatile Silicone

EXAMPLE 6

A coal tar stick was prepared using the procedures described in Example 1. A product was produced having the following composition (in weight percent):

2.0%	Coal Tar Extract
22.0%	Stearyl Alcohol

6.0% Cetyl Alcohol
.3% Preservatives
6.0% PEG-1000
63.7% Volatile Silicone

EXAMPLE 7

An antibiotic stick (using Bactimycin as the active ingredient) was prepared using the procedures described in Example 1. A product was produced having the following composition (in weight percent):

.5% Bactimycin
21.0% Stearyl Alcohol
6.0% PEG-1000
.5% Various preservatives
5.0% Cetyl Alcohol
67.0% Volatile Silicone

EXAMPLE 8

A hydrocortisone stick was prepared using the procedures described in Example 1. A product was produced having the following composition (in weight percent):

.5% Hydrocortisone
21.0% Stearyl alcohol
5.0% PEG-1000
5.0% Cetyl Alcohol
.5% Preservatives
.2% TEA-99%
67.8% Volatile Silicone

EXAMPLE 9

An antiseptic stick (using providone-iodine as the active ingredient) was prepared using the procedures described in Example 1. A product was produced having the following composition (in weight percent):

1.0% Providone-Iodine

20.0%	Stearyl Alcohol
8.0%	PEG-1000
.5%	Preservatives
5.0%	Cetyl Alcohol
.5%	Petrolatum
65.0%	Volatile Silicone

EXAMPLE 10

A 13-cis-retinoic acid stick for the treatment of acne, was prepared using the procedure described in Example I. A product having the following composition (in weight percent).

.10%	13-cis-Retinoic Acid
29.0%	Stearyl Alcohol
1.0%	Cetyl Alcohol
3.0%	Laureth-4
6.0%	Peg-1000
60.9%	Volatile Silicone

From the foregoing it becomes readily apparent that a novel and unique vehicle system has been herein described which delivers active pharmaceutical and cosmetic ingredients in a form wherein the bioavailability and percutaneous absorption are remarkably enhanced and with which the physical disadvantages of prior art systems have been obviated. Of course, such modifications, alterations and adaptations as will readily occur to the skilled artisan confronted with this disclosure are intended within the spirit of the present invention which is limited only by the scope of the claims appended hereto.

Claims.

1. An improved delivery system for presenting pharmaceutically active ingredients to the human skin for enhanced percutaneous adsorption and bioavailability comprising a mixture containing from about 20% up to about 40% (w/w) fatty alcohol having 12 to 22 carbon atoms or mixtures thereof; from about 30% up to about 60% (w/w) of a volatile silicone; from about 0.1% up to about 10% (w/w) of an active pharmaceutical ingredient selected from the group consisting of hydroquinone, benzoyl peroxide, hydrocortisone, providone-iodine, coal tar extract, and 13-cis-retinoic acid; and from about 1% to about 10% of an ingredient selected from a preservative, an emulsifier or a mixture thereof.

2. A system acccording to claim 1 in which said fatty alcohol comprises a mixture of stearyl and cetyl alcohol.

3. A system according to claim 1 in which said volatile silicone is cyclomethicone.

4. A system according to claim 1 in which said volatile silicone is dimethicone.

5. A system according to claim 3 in which said fatty alcohol comprises a mixture of stearyl and cetyl alcohol.

6. A system according to claim 4 in which said fatty alcohol comprises a mixture of stearyl and cetyl alcohol.

7. A pharmaceutical preparation for the treatment of hyperpigmentation consisting from about 0.1% up to about 10% (w/w) of hydroquinone as its essential ingredient, said ingredient dispersed throughout a semi-solid vehicle having from about 20% up to about 40%(w/w) stearyl and cetyl alcohol; from about 30% up to about 60% (w/w) of a volatile silicone; and from about 1% to about 10% w/w of an ingredient selected from a preservative, an emulsifier or a mixture thereof.

8. A pharmaceutical preparation according to claim 7 in which said volatile silicone is cyclomethicone.

9. A pharmaceutical preparation having enhanced bioavailability and percutaneous adsorption for the treatment of acne consisting of from about 0.1% up to about 10% (w/w) of a compound selected from the group consisting of benzoyl peroxide and 13-cis retinoic acid as its essential active ingredient, said ingredient being disposed throughout a semi-solid vehicle having from about 20% up to about 40% (w/w) stearyl and cetyl alcohol; from about 30% up to about 60% (w/w) of a volatile silicone; and from about 1% to about 10% (w/w) of an ingredient selected from a preservative, an emulsifier or a mixture thereof.

10. A pharmaceutical preparation according to claim 9 in which said volatile silicone is cyclomethicone.

11. A pharmaceutical preparation having enhanced bioavailability and percutaneous adsorption consisting of from about 0.1% up to about 10% (w/w) of active ingredients selected from the group consisting of hydroquinone, benzoyl peroxide, hydrocortisone, providone-iodine, coal tar extract, bactimycin, and 13-cis-retinoic acid, said ingredient being dispersed throughout a semi-solid vehicle having from about 20% up to about 40%(w/w) stearyl and cetyl alcohol; from about 30% up to about 60% (w/w) of a volatile silicone; and from about 1% to about 10% w/w of an ingredient selected from a preservative, an emulsifier or a mixture thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US85/00172

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC [4]

INT. CL. A61K 7 /135; A61K 31/74; A61K 31/615; A61K 31/12; A61K 31/07
U.S. CL. 62 ; 78 ; 233 ; 331 ; 344

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/62, 78, 233, 331, 344

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US, A, 3,836,647, Lange, 17/September, 1974, column 7, lines 15 to 57 and column 8, lines 1 to 4	1 to 11
X	US, A, 3,856,934, Kligman, 24/December, 1974, column 4, lines 34 to 44	1 to 11
X	US, A, 3,906,108, Fe ty, 16/September, 1975, column 4, lines 38 to 54	1 to 11
X	US, A, 4,322,438, Peck, 30 March, 1982, column 1, lines 34 to 43	1 to 11
X	GB, A, 803,289, Senior, 22/October, 1958, column 6, lines 78 to 87	1 to 11
X	GB, A, 1,206,790, Gueyne et al, 30/September 1970, column 9, lines 19 to 40	1 to 11

* Special categories of cited documents: [15]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
30 March 1985	22 APR 1985
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/USA	Dale R. Ore

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